



I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: 8/27/04

Signature: Valerie J. Sarosky

(Valerie J. Sarosky)

Docket No.: TUU-P01-006  
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:  
Bachovchin et al.

Application No.: 09/628225

Art Unit: 1654

Filed: July 28, 2000

Examiner: J. E. Russel

For: METHOD OF REGULATING GLUCOSE  
METABOLISM, AND REAGENTS RELATED  
THERE TO

**SUBMISSION OF DECLARATIONS UNDER 37 CFR 1.131**

MS Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:


**INTRODUCTORY COMMENTS**

In response to the Examiner's statement that the declaration by Drucker under 37 CFR 1.131 is insufficient to antedate either the Balkan et al. abstract or the German patent '486 since the declaration is not signed by all of the inventors of the claimed subject matter, Applicants enclose corresponding declarations under 37 CFR 1.131 by coinventors Plaut and Bachovchin.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. TUU-P01-006 from which the undersigned is authorized to draw.

Dated: August 27, 2004

Respectfully submitted,

By 

David P. Halstead

Registration No.: 44,735  
ROPES & GRAY LLP  
One International Place  
Boston, Massachusetts 02110-2624  
(617) 951-7000  
(617) 951-7050 (Fax)  
Attorneys/Agents For Applicant



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:  
Bachovchin

Serial No: 09/628,225

Filed: July 28, 2000

For: Method of Regulating Glucose  
Metabolism, And Reagents Related  
Thereeto

Attorney Docket No. TUU-P01-006

Art Unit: 1654

Examiner: J. Russel

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**Declaration Under 37 CFR 1.131 of William W. Bachovchin**

Sir:

I, William W. Bachovchin of Melrose, Massachusetts, hereby declare as follows:

1. I am a co-inventor of the above-mentioned application which teaches and claims uses of dipeptidylpeptidase IV inhibitors for treatment of Type II diabetes, modifying GLP-1 metabolism, and modifying glucose metabolism, among other things.
2. The invention as described and claimed in the above-identified application was conceived prior to the publication of Balkan et al., Diabetologia, Suppl 40, A131 Abstract, which published in June of 1997.
3. In support of this, I attach as Exhibit A the text of an e-mail from coinventor Daniel Drucker to coinventor Andrew Plaut memorializing our decision to administer Pro(boro)Pro in an oral glucose tolerance test (OGTT) in mice to confirm its effectiveness for treating Type II diabetes, modifying GLP-1 metabolism, or modifying glucose metabolism, an invention of which I contributed to the conception. See Exhibit B for the structure of Pro(boro)Pro. This compound is a potent dipeptidylpeptidase IV inhibitor. The OGTT in this case measures the efficacy of Pro(boro)Pro in reducing blood glucose levels when administered to mice that had ingested a measured amount of glucose after a period of fasting. The e-mail of Exhibit A was sent prior to June 1997.
4. Type II diabetes is characterized by glucose intolerance. The mice used in our experiments are reasonable models of glucose intolerance.
5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United

States Code and that willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

William W. Bachovchin

Dated:

Signature:

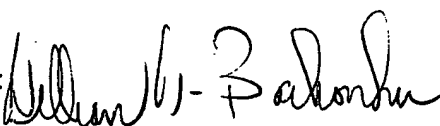
A handwritten signature in black ink, appearing to read 'William W. Bachovchin', written over the printed name and the 'Signature:' label.



Exhibit A

From: IN%"d.drucker@utoronto.ca" 12-MAY-1997

Hi Anfrew,

I may have met a very distant cousin of yours in Baltimore (Allergy and Immunology, now at the NIH?) this weekend.

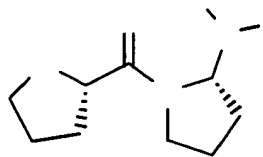
On perusing the papers you sent me, the best experiments would be those we could carry out in rats. This is because a) rats have higher levels of DP-IV than mice and b) we could get more blood from the rats for HPLC/RIA experiments to show the precise molecular forms of peptides in the presence and absence of inhibitors. Any data on the use of the inhibitors in rats from your group? I am extrapolating from the []s of inhibitor used in mice as follows, so correct me if I make a mistake: The [] of inhibitor that is reasonably effective is 1 ug/kg sc twice a day.

If we do rats, then this would be ~250 ug twice a day, x 10 rats for example, x 10 days (for the bowel growth/GLP-2 effects). Do you have these amounts of inhibitor available? If so, we could try and get these studies done in the next few months. We could also do some more acute effects with OGTT and GLP-1 that would be short-term studies that wouldn't require much inhibitor. Let me know if the amount of material required is a problem. DD

\*\*\*\*\*Daniel

Drucker M.D.                      416-340-4125 voice      416-978-4108 Fax  
Director, Endocrine Division  
Department of Medicine  
University of Toronto  
The Toronto Hospital  
200 Elizabeth Street CCRW3-838  
Toronto, Ontario Canada M5G 2C4

**Exhibit B**



Pro(boro)Pro



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:  
Bachovchin

Serial No: 09/628,225

Filed: July 28, 2000

For: Method of Regulating Glucose  
Metabolism, And Reagents Related  
Thereeto

Attorney Docket No. TUU-P01-006

Art Unit: 1654

Examiner: J. Russel

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**Declaration Under 37 CFR 1.131 of Andrew G. Plaut**

Sir:

I, Andrew G. Plaut of Lexington, Massachusetts, hereby declare as follows:

1. I am a co-inventor of the above-mentioned application which teaches and claims uses of dipeptidylpeptidase IV inhibitors for treatment of Type II diabetes, modifying GLP-1 metabolism, and modifying glucose metabolism, among other things.
2. The invention as described and claimed in the above-identified application was conceived prior to the publication of Balkan et al., Diabetologia, Suppl 40, A131 Abstract, which published in June of 1997.
3. In support of this, I attach as Exhibit A the text of an e-mail from coinventor Daniel Drucker to me memorializing our decision to administer Pro(boro)Pro in an oral glucose tolerance test (OGTT) in mice to confirm its effectiveness for treating Type II diabetes, modifying GLP-1 metabolism, or modifying glucose metabolism. See Exhibit B for the structure of Pro(boro)Pro. This compound is a potent dipeptidylpeptidase IV inhibitor. The OGTT in this case measures the efficacy of Pro(boro)Pro in reducing blood glucose levels when administered to mice that had ingested a measured amount of glucose after a period of fasting. I received the e-mail of Exhibit A prior to June 1997.
4. After sending the e-mail of Exhibit A, I sent a batch of Pro(boro)Pro to co-inventor Daniel Drucker prior to June 1997. (See Exhibit C)
5. Type II diabetes is characterized by glucose intolerance. The mice used in our experiments are reasonable models of glucose intolerance.
6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these

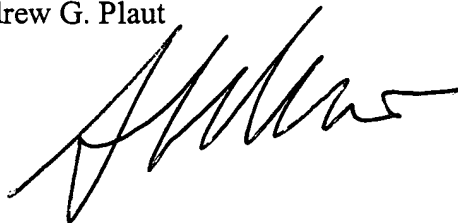
statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code and that willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Andrew G. Plaut

Dated:

August 1, 2004

Signature:

A handwritten signature in black ink, appearing to read 'A. Plaut', written over a horizontal line.





**Exhibit A**

From: IN%"d.drucker@utoronto.ca" 12-MAY-1997

Hi Anfrew,

I may have met a very distant cousin of yours in Baltimore (Allergy and Immunology, now at the NIH?) this weekend.

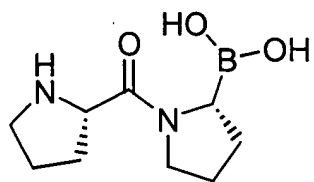
On perusing the papers you sent me, the best experiments would be those we could carry out in rats. This is because a) rats have higher levels of DP-IV than mice and b) we could get more blood from the rats for HPLC/RIA experiments to show the precise molecular forms of peptides in the presence and absence of inhibitors. Any data on the use of the inhibitors in rats from your group? I am extrapolating from the []s of inhibitor used in mice as follows, so correct me if I make a mistake: The [] of inhibitor that is reasonably effective is 1 ug/kg sc twice a day.

If we do rats, then this would be ~250 ug twice a day, x 10 rats for example, x 10 days (for the bowel growth/GLP-2 effects). Do you have these amounts of inhibitor available? If so, we could try and get these studies done in the next few months. We could also do some more acute effects with OGTT and GLP-1 that would be short-term studies that wouldn't require much inhibitor. Let me know if the amount of material required is a problem. DD

\*\*\*\*\*Daniel

Drucker M.D.                      416-340-4125 voice      416-978-4108 Fax  
Director, Endocrine Division  
Department of Medicine  
University of Toronto  
The Toronto Hospital  
200 Elizabeth Street CCRW3-838  
Toronto, Ontario Canada M5G 2C4

**Exhibit B**



Pro(boro)Pro

**Exhibit C**

May 19, 1997

Dr. Daniel Drucker, Director  
Division of Endocrinology  
Department of Medicine  
University of Toronto  
The Toronto Hospital  
200 Elizabeth St.  
CCRW3-838  
Toronto Ontario CANADA  
M5G 2C4

Voice mail: (416) 340-4125  
FAX (416) 978-4108

Dear Dan,

Enclosed is 15 mgm of Pro(boro)Pro, the DPIV inhibitor. Suggestions for storage were sent by e-mail.

Good luck.

Sincerely yours,

Andrew G Plaut, MD